UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,803	04/13/2007	Robert Tridgett	3073.007A	6534

23405 7590 01/29/2009

HESLIN ROTHENBERG FARLEY & MESITI PC
5 COLUMBIA CIRCLE
ALBANY, NY 12203

EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
01/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,803	TRIDGETT ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-57* is/are pending in the application.

4a) Of the above claim(s) *37,40,41,43-46 and 50-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,36,38,39,42 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 35-57 are currently pending. Claims 51-57 are withdrawn. Additionally, claims 37, 40-41, 43-46 and 50 which are drawn to a non-elected species are withdrawn. And claims 1-34 are cancelled. Accordingly, claims 35-36, 38-39, 42 and 47-49 are the subject of this Office Action. This is the first Office Action on the merits of the claims.

Election/Restrictions

2. Applicant's election of Group I in the reply filed on 12/24/2008 is acknowledged. Applicant traverses on the grounds that it would not be an undue burden to examine the claims of Group I and Group II together. A serious search and examination burden if restriction were not required can be shown when one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

In the instant case, a search for Group I would require a different field of search and the prior art applicable to Group I would not likely be applicable to a search of Group II. Specifically, a search for the compounds and compositions of Group I would not encompass a search for the chemical synthesis of compounds of Group I.

3. The requirement is still deemed proper and is therefore made FINAL.

4. Applicant's election of the *2S*,3*S*,11b*R* isomer compound specie and acid addition salt in the reply filed on 12/24/2008 is also acknowledged. The elected species read upon claims 35-36, 38-39, 42 and 47-49.

5. Claims 37, 40-41 and 43-46 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on 12/24/2008.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

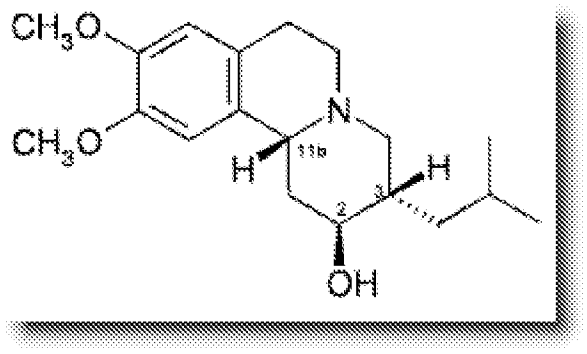
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. **Claims 35 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Kilbourn et al* (Eur J Pharmacol, 278:249-252, 1995) as evidenced by *Williams et al* (Foye's Principles of Medicinal Chemistry, Page 50, 2002)**.

9. Instant claim 35 is drawn to 3,11b-*cis*-dihydrotetrabenazine or a salt thereof, more specifically in the form of a *2S*,3*S*,11b*R* isomer having the following formula



as elected by Applicant, which reads on claims 35 and 42.

10. Dihydrotetrabenazine is well known in the art and, as disclosed by *Kilbourn et al*, "contains three asymmetric carbon centers (C-2, C-3 and C-11b). The two isomers at the C-2 carbon can be easily resolved by column chromatography and are termed α- and β- dihydrotetrabenazine… For α- dihydrotetrabenazine, with two asymmetric centers, there are four possible isomers" (Page 249, Column 2). Accordingly, one of ordinary skill in the art would understand that β-dihydrotetrabenazine similarly contains two asymmetric centers and thus also has four possible isomers. As such, one of

ordinary skill in the art would recognize that dihydrotetrabenazine has eight possible isomers which can be immediately envisaged as (1) *2S*,3*S*,11b*S*, (2) ***2S*,3*S*,11b*R***, (3) *2S*,3*R*,11b*S*, (4) *2S*,3*R*,11b*R*, (5) *2R*,3*S*,11b*S*, (6) *2R*,3*S*,11b*R*, (7) *2R*,3*R*,11b*S*, and (8) *2R*,3*R*,11b*R* (Applicant's elected specie in bold). However, *Kilbourn et al* do not explicitly disclose Applicant's elected specie.

11. It is well known that a single isomer is often therapeutically superior to the racemic mixture and to the other isomers. The potential advantages include (1) improved therapeutic index through increased potency and selectivity and decreased side-effects; (2) improved onset and duration of effect; and (3) decreased propensity for drug-drug interactions. Indeed, as taught by *Williams et al*, discussing compounds that are combinations of isomers: "when introduced into an asymmetric, or chiral, environment, such as the human body, enantiomers will display different physical chemical properties producing significant differences in their pharmacokinetic and pharmacodynamic behavior. Such differences can result in adverse side effects or toxicity dues to one of the isomers or the isomers may exhibit significant differences in absorption, serum protein binding, and metabolism" (Page 50, Column 1). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to produce the *2S*,3*S*,11b*R* isomer as recited by the instant claims. The skilled artisan would have predicted that the *2S*,3*S*,11b*R* isomer would likely possess properties similar to those exhibited by the racemic mixture and trans isomers disclosed by *Kilbourn et al*, and potentially superior properties as discussed above; thus, the skilled artisan would have been motivated to produce the *2S*,3*S*,11b*R* isomer

in order to determine whether the *2S*,3*S*,11b*R* isomer does indeed exhibit superior properties (e.g., increased potency and selectivity, decreased side-effects, improved onset and duration, reduced drug-drug interactions, etc). "A known compound may suggest its analogs or isomers, either geometic isomers (cis v. trans) or position isomers (e.g., ortho v. para)" *In re Deuel*, 51 F.3d 1552, 34 USPQ 2d 1210, 1214 (Fed Cir 1995). Accordingly, instant claims 35 and 42 are rejected as *prima facie* obvious.

12. **Claims 36, 38-39 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Kilbourn et al* (Eur J Pharmacol, 278:249-252, 1995) as applied to claims 35 and 42 above, in view of *Reich et al* (US 6,462,069)**.

13. Instant claims 36 and 38-39 are drawn to compositions consisting of (claim 36) or comprising (claims 38-39) 3,11b–cis-dihydrotetrabenazine in substantially pure form (claim 36), being substantially free of 3,11b-trans-dihydrotetrabenazine (claim 38) or containing less than 5% of of 3,11b-trans-dihydrotetrabenazine (claim 39).

14. As discussed above, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to produce the cis isomer of dihydrotetrabenazine in an effort to identify a compound exhibiting desirable properties such as increased potency and selectivity, decreased side-effects, improved onset and duration, reduced drug-drug interactions, etc as compared to racemic dihydrotetrabenazine or other isomers of dihydrotetrabenazine. Furthermore, it would have been obvious to a person of ordinary skill in the art to formulate the compositions consisting of or comprising the cis isomer wherein the isomer is in substantially pure form as recited by instant claims 36 and 38-39. As disclosed by *Reich et al* (who teach

compositions comprising amino-pyrazole compounds), "[a]s generally understood by those skilled in the art, an optically pure compound having one chiral center (i.e., one asymmetric carbon atom) is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diasteromerically pure and entiomerically pure" (Column 15, Line 62 - Column 16, Line 1). Moreover, *Reich et al* teach that compounds most preferably are used in a form that is at least 99% of a single isomer (98% entiomeric excess or diastereomeric excess) (Column 16, Lines 7-8). As such, it would have been obvious to a person of ordinary skill in the art to formulate the composition consisting of or comprising the isomer in a substantially pure form (as recited by instant claim 36), being substantially free of the trans isomer (as recited by instant claims 38 and 39).

15. Instant claim 49 is drawn to a pharmaceutical composition comprising 3,11b-cis-dihydrotetrabenazine or a salt thereof and a pharmaceutically acceptable carrier. As discussed above, *Kilbourn et al* teach pharmaceutical compositions comprising a *trans* dihydrotetrabenazine isomer strongly binds VMAT2 (entire document). Accordingly, the skilled artisan would have been motivated to formulate pharmaceutical compositions comprising the *2S*,3*S*,11b*R* cis isomer to determine whether it can bind VMAT2 with increased potency and selectivity, decreased side-effects, improved onset and duration, reduced drug-drug interactions, and so on. Additionally, although *Kilbourn et al* do not explicitly teach the inclusion of a pharmaceutically acceptable carrier, *Kilbourn et al* disclose that the pharmaceutical compositions “were injected via the tail vain” (Page

250, Column 2). Since it is unclear how an injectable composition could not include a pharmaceutically acceptable carrier, it is asserted that, absent evidence to the contrary, the composition of *Kilbourn et al* necessarily includes a pharmaceutically acceptable carrier.

16. **Claims 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Kilbourn et al* (Eur J Pharmacol, 278:249-252, 1995) as applied to claims 35 and 42 above in view of *Berge et al* (J Pharm Sci 66:1-19, 1977).**

17. Instant claims 47-48 are drawn to the compound of claim 35 in the form of an acid addition salt (claim 47), more specifically wherein the salt is a methane sulphonate salt (claim 48). As taught by *Berge et al*, "[t]he chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form" (Page 1, Column 1). More specifically, *Berge et al* disclose that methanesulfonic acid is a potentially useful salt form of pharmaceutical agents (Page 5, Table III). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to formulate the isomer as a mesylate salt. The skilled artisan would have been motivated to do in order to optimize the chemical, biological, physical and economic characteristics of the compound in view of *Berge et al*.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-

5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614